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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,988	08/08/2006	Warren J. Leonard	252024	4910

45733 7590 04/16/2009

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EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,988	LEONARD ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,8,10-12,18,20 and 32-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,8,10-12,18,20,32-35* is/are rejected.

7)☒ Claim(s) *33, 35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02-04-2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02-04-2009 has been entered.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Claims 5, 8, 10-12, 18, 20 and 32-35 are pending. Claims 5 and 18 have been amended by Applicant's amendment filed on 02-04-2009.
4. Accordingly, claims 5, 8, 10-12, 18, 20 and 32-35 are currently under examination to which the following grounds of rejection are applicable.

Response to Applicant's Remarks

Objections/rejections maintained in response to Applicant arguments or amendments:

Claim Rejections - 35 USC § 112 - written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 5, 8, 10-12, 18, 20 and 32-35 remain rejected under 35 U.S.C. 112, first paragraph,

as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 5, 8, 10-12, 18, 20 and 32-35 as best understood, are readable on a genus of IL-21 polypeptide variants of SEQ ID No. 1 comprising 1, 2, 3, 4 or 5 amino acid substitutions, deletions or addition at any location of the polypeptide sequence of SEQ ID No. 1, said polypeptide variants functionally able to contact a population of cells comprising a mature B cell and a B cell progenitor cell to induce differentiation of said B cell populations into a memory B cell and a plasma cell, respectively, so as to enhance an immune response in a subject (e.g., against an antigenic viral, tumor or bacterial epitope) when introduced into a subject, wherein the genus of nucleic acids is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made. The polypeptide variants of SEQ ID NO: 1 with 1 to 5 amino acid substitutions, deletions or addition, when given the broadest reasonable interpretation, encompass unspecified variants of polypeptides of any undetermined length which can be fragments with or without the claimed functionality of binding the IL-21 receptor to induce differentiation of at least one or more mature B cell and a B cell progenitor cell into one or more of a memory B cell and a plasma cell. Note that SEQ ID No. 1 is a 160-aa residue polypeptide. Thus the claims encompass variants of SEQ ID No. 1 at least 96.8% identical to SEQ ID No 1. The specification and claims do not place any limits on the

location of 1 to 5 amino acid changes relative to the full length of SEQ ID No. 1 or whether the aa changes are clustered or separated.

Applicant, provides one example of IL-21 protein, i.e., a human IL-21 of 160-aa residue (100 ng/ml, R&D systems, Minneapolis, MN) . SEQ ID NO: 1 is the amino acid sequence of human IL-21. Thus the specification provides sufficient description for the human IL-21 (100 ng/ml, R&D systems, Minneapolis, MN) of SEQ ID No 1. However, the description of one human IL-21 that induces maturation of B cells accompanied by class switching and plasma formation *in vitro*, is not representative of the entire genus unspecified variants of IL-21 of SEQ ID No. 1 with 1 to 5 amino acid substitutions, deletions or addition. Moreover, the specification discloses at pages 30-34, that "IL-21 polypeptides (including variant polypeptides and IL-21 polypeptide analogs, such as IL-21 agonists), can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, can contain amino acids other than the 20 gene-encoded amino acids, contain alterations which produce silent substitutions, additions, or deletions, and others (p. 30, lines 10-31; p. 31, lines 1-13).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to

show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

The specification discloses at page 45, lines 21-26, in *vivo* transient expression of IL-21 wherein the murine IL-21 cDNA was cloned into a vector and injected intravenously into mice. Murine cell population was evaluated to determine IL-21 apoptotic effect (Example 2). Moreover, transgenic mice expressing human IL-21 were generated and splenocytes from the human IL-21 transgenic mice were analyzed by FACS with antibodies to surface markers including CD21, IgM, and IgD to evaluate number of mature B cells (Example 3, particularly, p. 50, lines 8-12). Example 4 discloses *in vitro* effect of IL-21 on murine isolated B cells, from direct stimulation of B cells with IL-21, in the presence of anti-CD40, in combination with either IL-4, anti-CD40, or both stimuli (p. 53, lines 10-15). FACS analysis illustrates that B cells contacted with IL-21, in the presence of anti-CD40, in combination with either IL-4, anti-CD40, or both stimuli resulted in IL-21 induced expression of sydecan-1 (a plasma marker) and induced expression of surface IgG (Fig. 6B and Fig. 6C), which overall indicates that IL-21 " induces an increase in immature B cells, alters the B cell phenotype and is a potent inducer of B cell maturation to memory B/post-switch cells and plasma cells. IL-21 also induces differentiation of human B cells into plasma cells (FIG. 8) and memory B cells "(p. 53, lines 23-26). However, the specification does not teach regions or domains of the polypeptide of SEQ ID No. 1 essential for binding the IL-21 receptor to induce differentiation of at least one or more mature B cell and a B

cell progenitor cell into one or more of a memory B cell and a plasma cell. At the time the invention was made, it was well known in the art that certain positions in the sequences of peptides/proteins are critical to the protein's structure/function relationship, particularly, various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (Guo et al.,.Proc Natl Acad Sci U S A. 2004 101:9205-10; p. 9209, col. 1, last paragraph). The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry John Wiley and Sons, 1990, p. 126-129). Even single-nucleotide polymorphism without affecting the amino acid sequence can affect folding of the protein and thus alter its function (Kimchi-Sarfaty et al., 2007, Science, pp. 525-528; p. 527, col. 3, last paragraph). There is no structure/function relationship taught at all for claimed variants and fragments other than the full length of SEQ ID No. 1. There is not disclosure of residues in the binding pocket of the SEQ ID No. 1 that are critical for binding the IL-21 receptor resulting in the claimed activity. This may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site for the polypeptide of SEQ ID No. 1 must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues of amino acids of the binding pocket. Further, there is no teaching of how many amino acids may be modified from in the 160-aa polypeptide sequence of SEQ ID No 1 to retain function. This

disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims, as one of skill in the art cannot envision all the polypeptide fragments having at least 96.4% or greater sequence identity to SEQ ID No. 1 able to bind the IL-21 receptor to induce differentiation of at least one or more mature B cell and a B cell progenitor cell into one or more of a memory B cell and a plasma cell based on the teachings in the specification. Thus, it is not possible from reading the examples to envision what type of mutations have been introduced, or how many mutations have been introduced in each modified SEQ ID No. 1 that is at least of 96.4% or greater homology to SEQ ID NO: 1 or which genes have incurred mutations to result in differentiation of at least one or more mature B cell and a B cell progenitor cell into one or more of a memory B cell and a plasma cell. Neither applicants nor the prior art disclose other isolated nucleic acid molecules encoding for human IL-21 binding the IL-21 receptor to induce differentiation of at least one or more mature B cell and a B cell progenitor cell into one or more of a memory B cell and a plasma cell.

In conclusion, Although sufficient description is given for a composition comprising the amino acid of SEQ ID No. **1**, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a genus of nucleic acid sequences encoding a IL-21 polypeptide being at least 96.4% identical to the polypeptide of SEQ ID No. 1. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Response to Applicants' Arguments as they apply to rejection of Claims 5, 8, 10-12, 18, 20 and 32-35 under 35 U.S.C. 112, first paragraph-written description.

At page 6 of remarks, Applicants essentially argue that the specification provides sufficient guidance for amino acid variants of SEQ ID NO:1 containing 160 aa of at least 96% identity to SEQ ID No. 1. Moreover, Applicants allege that support is found in U.S. Patent Application Publication 2003/0003545 (Ebner et al.) for the disclosure of variants that differ from IL-21, but retain the essential properties thereof as Ebner et al. discloses conserved regions of IL-21 polypeptide in Figures 1, 4, 6A- B, and 7, and Tables I-III. Furthermore, Ebner et al. discloses regions of identity between IL- 21 and other interleukins in Figures 3A-C. As such applicants contend that regions of IL-21 polypeptide that should not be mutated were known in the art. Furthermore, Applicants allege at page 6 of Remarks that sufficient guidance is provided in the specification for assays to determine suitable variants including binding assays, real-time PCR and assays to test signaling pathways induced by binding of IL-21 to its receptor. Such is not persuasive.

The examiner refers applicants to the reasons already of record as discussed at pages 8 and 9 of the office of 09-08-2008 essentially stating that US Publication No. 20030003545 discloses one species of IL-21, i.e., the nucleotide sequence of SEQ ID No. 1 and the corresponding encoded amino acid sequence of SEQ ID No. 3 with the description of conserved domains (e.g., Fig. 1) and sequence identity with hIL-17, mIL-17, viral IL-17, IL-20 and others. In addition US Publication No. 20030003545 merely discloses at page 9, paragraph [0073], "one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function". It is unclear how the functional secretory function of SEQ ID No. 3 of US Publication No. 20030003545 relates to the instantly claimed binding domain of SEQ ID No. 1, or how modification of the N-terminus or C-terminus amino

acid sequence of instantly claimed SEQ ID No. 1 affect the functionality of the protein. Furthermore, the contemplation of the claimed genus of assays to determine suitable variants of at least 96.8% identity to SEQ ID No. 1 is not sufficient to support the present claimed invention as the guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention.

Claim Rejections - 35 USC § 112 - enablement

To the extent that the claims read on an *ex vivo* method for enhancing an immune response in a subject or treating a subject with a deficiency of at least one memory B cell and plasma cell, the following rejection apply.

Claims 5, 8, 10-12, 18, 20 and 32-35 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for claims directed to an *ex vivo* method of enhancing an immune response to a viral antigen or treating a subject with a condition comprising a specific deficiency of at least one of memory B and plasma cells comprising isolating a population of cells from the subject having one or more of a mature B cell and a cell progenitor, contacting said population with IL-21 of SEQ ID No. 1 or a genus of IL-21 polypeptide variants of SEQ ID No. 1 comprising 1, 2, 3, 4 or 5 amino acid substitutions, deletions or addition, so as to induce differentiation of said B cells into a memory B cell and a

plasma cell, respectively, wherein the population is optionally contacted with an antigen, isolating said memory B cell and plasma cell and introducing said cell population into the subject.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The specification does not reasonably provide enablement for using *ex vivo* methods of therapy by introducing host cells exposed *ex vivo* to Il-21 into the body of the subject so as to achieve an immune response against an intracellular viral pathogen, as the specification provide insufficient guidance for issues related to treatment of viral infection. Moreover, the specification does not reasonably provide enablement for claims directed to a composition comprising a genus of variants of SEQ ID No. 1 comprising 1, 2, 3, 4 or 5 amino acid substitutions, deletions or addition. Thereby, specific issues including issues related to immune responses against intracellular pathogens such as viruses and differentiation of a mature B cell and a B cell progenitor cell into a memory B cell and a plasma cell after contacting of said population of cells with unspecified variants of polypeptides of SEQ ID No. 1 of any undetermined length which

can be fragments with or without the claimed functionality of binding the IL-21 receptor, have to be examined and considered for patentability regarding the broadly claimed methods.

The specification as filed discloses at page 45, lines 21-26, in *vivo* transient expression of IL-21, wherein the murine IL-21 cDNA was cloned into a vector and injected intravenously into mice. Murine cell population was evaluated to determine IL-21 apoptotic effect (Example 2). Moreover, transgenic mice expressing human IL-21 were generated and splenocytes from the human IL-21 transgenic mice were analyzed by FACS with antibodies surface markers including CD21, IgM, and IgD to evaluate number of mature B cells (Example 3, particularly, p. 50, lines 8-12). Example 4 discloses *in vitro* effect of IL-21 on murine isolated B cells, from direct stimulation of B cells with IL-21, in the presence of anti-CD40, in combination with either IL-4, anti-CD40, or both stimuli (p. 53, lines 10-15). FACS analysis teach that B cells contacted with IL-21, in the presence of anti-CD40, in combination with either IL-4, anti-CD40, or both stimuli resulted in IL-21 induced expression of sydecan-1 (a plasma marker) and induced expression of surface IgG (Fig. 6B and Fig. 6C), which overall indicates that IL-21 " induces an increase in immature B cells, alters the B cell phenotype and is a potent inducer of B cell maturation to memory B/post-switch cells and plasma cells. IL-21 also induces differentiation of human B cells into plasma cells (FIG. 8) and memory B cells "(p. 53, lines 23-26).

In relation to enhancing an immune response against a viral antigen, the art teaches that humoral immunity (e.g. Ab production by plasma cells) is effective specifically for extracellular pathogens and antigens (e.g., gram positive bacteria, toxins). However, viruses are intracellular pathogens (grow inside cells of the host). When viruses are inside cells they are not accessible to Ab, only when they are outside in the body fluids they are exposed to antibodies. Therefore, the

immune system responds to intracellular viruses to induce an immune response against them by engaging both humoral and cellular immune responses. Moreover, generation of CD8+T cytotoxic cell, involved in cell-mediated immunity, is critical for immune responses against intracellular viruses (Immunology Lectures notes, 2002, School of Medicine USUHS, pp. 113-122). The art of record also discloses a divergent number of microbial infections with different antigenic properties as shown by their mechanism of depressing the immune responses in a subject (Mims et al., Medical Microbiology, 2004; pp 172-177). Moreover, the art at the time the invention was made teaches that interaction between CD40 and CD40L during T and B cell contact is essential for all events in thymus-dependent antigen responses such as Ig production, isotype switching, somatic hypermutation and induction of B cell memory (Lee et al., *Proc Natl Acad Sci* 1999:9136-41; p. 9136, col. 1). Hence the art discloses that T-B collaboration is essential for B cell expansion and diversification of the Ig receptor. The specification discloses the effect of IL-21 on *in vitro* B cell maturation, from direct stimulation of B cells by IL-21, in the presence of anti-CD40, in combination with either IL-4, anti-CD40, or both stimuli (p. 53, lines 10-15). These responses lead to antibodies production by B cell, which ultimately recognize native, soluble antigens. However, viral antigens are also processed on the surface of host cells in association with MHC I molecules eliciting a cell mediated immune response. Thus both B cell and T cells are involved in the immune response against a viral antigen. The instant claims broadly embrace a method for enhancing an immune response against a viral antigen that merely requires contacting a population of mature B cells and B cell progenitor with IL-21 even without exposure to a viral antigen which are able, when introduced in a subject, to enhance the response against a viral antigen. However, the art teaches that humoral responses are not effective against

intracellular pathogens but only against pathogens that are in extracellular fluids. Thus, it is not apparent how one skilled in the art would reasonably believe, without any undue experimentation, that introducing into a subject a differentiated population of a memory B cell and plasma cell that merely neutralizes extracellular invading pathogens, would effectively treat or enhance an immune response against any intracellular viral antigen specific to the viral infection to be treated without co-exposure of said B cell population to a viral antigen, particularly given the interaction of both B and T cells immune responses as taught by the art, and the lack of working examples for an *ex vivo* method as broadly claimed. There is not disclosure in the specification as filed of any *in vivo* production of immunoglobulin G by plasma cells or how memory B cells no exposed to an antigen are able to elicit a humoral response after a secondary exposure to an Ag let alone enhancing an immune response in a subject by secretion of specific neutralizing antibodies. It is noticed that post-filing art only discloses *ex vivo* therapy methods in relation to enhancement on tumor-specific $CD8^+$T cell responses by IL-21 and not IL-21 enhancement of B-cells against a viral antigen. For example, post-filing art of Moroz et al., (2004, J. Of Immunology, pp.900-909), teaches the anti-tumor activity of IL-21 injected i.p. using *ex vivo* therapy methods in mice injected through the tail vein with $3x10^6$ cells $CD8^+$T cells and challenged one day latter with syngeneic E.G7 thyoma tumor cells. The anti-tumor activity of IL-21 correlates with the accumulation of tumor-specific $CD8^+$T cells that possessed increased cytolytic activity and that persisted in lymphoid tissues for several weeks (p. 901, col. 1, paragraphs 1 and 2). The author teaches that elimination of these cells (e.g., tumor-specific $CD8^+$T cells) abrogates mouse survival and abolished the induction of memory by IL-21 as measure by the ability to reject subsequent challenges (Moroz et al., 2004, J. of Immunology, p.

Comment [a1]: what does this have to do with inducing differentiation of B cells to memory or plasma type B cells?? Or the treatment of viral infection which is what they elected as the species of antigen. This reference teaches that IL-21 enhances CD8+ T cell activity and induces memory CD8+ T cells- this has nothing to do with B cells.

907; Sivkumar et al., Immunology, 2004, pp117-182; p. 180, col. 2, last paragraph). These observations are critical as Applicants have not provide evidence of *ex vivo* treatment of any virally infected subject with the claimed composition and the art discloses that treatment of various virally infected subjects including HIV-1 infection is not effective by merely eliciting humoral-mediated immune responses. In addition, it is not clear how B memory cell can become Ab-secreting cells without Ag exposure to specifically neutralize immunogenic epitopes of viral envelope proteins. As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to extensively test the claimed compositions as claimed.

Regarding the claimed invention drawn to a genus of polypeptides variants of SEQ ID No. 1 of at least 96.8% or greater identity to the polypeptide of SEQ ID No 1 exhibiting the claimed functionality of binding the IL-21 receptor to induce differentiation of at least one or more mature B cell and a B cell progenitor cell into one or more of a memory B cell and a plasma cell, the specification does not teach regions or domains of the polypeptide of SEQ ID No. 1 essential for binding the IL-21 receptor to induce differentiation of at least one or more mature B cell and a B cell progenitor cell into one or more of a memory B cell and a plasma cell. Note that SEQ ID No. 1 is a 160-aa polypeptide sequence. Thus the claims encompass variants of SEQ ID No. 1 at least 96.8% or greater identity to SEQ ID No 1. The specification and claims do not place any limits on the location of 1 to 5 amino acid changes relative to the full length of SEQ ID No. 1 or whether the amino acid changes are clustered or separated. There is not disclosure of residues in the binding pocket of the SEQ ID No. 1 that are critical for binding the IL-21 receptor. Neither

applicants nor the prior art disclose other isolated nucleic acid molecules encoding the human IL-21 of SEQ ID No. 1 able to bind the IL-21 receptor with the claimed activity. Applicant has provided little or no guidance beyond the mere enumeration of IL-21 polypeptide variants, especially conservative variants having only a small number of, such as 1 or 2 or 3, amino acid substitutions, relative to a naturally occurring IL-21 that can be employed in the claimed methods. Since, the relationship between sequences of nucleic acid/polypeptides and their secondary/tertiary structures sequence is not well understood and is not predictable, it would required undue experimentation for one skilled in the art to arrive at the isolated single nucleic acid sequence (e.g., DNA) encoding a polypeptide of at least 96.8% or greater sequence identity to SEQ ID No. 1 to bind the IL-21 receptor to induce differentiation of at least one or more mature B cell and a B cell progenitor cell into one or more of a memory B cell and a plasma cell. The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Even single-nucleotide polymorphism without affecting the amino acid sequence can affect folding of the protein and thus alter its function (Kimchi-Sarfaty et al., 2007, Science, pp. 525-528; p. 527, col. 3, last paragraph). While one of skill in the art can readily envision numerable species of polypeptides of at a given % identity to a recited reference amino acid sequence (e.g., SEQ ID No. 1), one cannot envision which of these also encode a polypeptide with a specified activity. In the instant case, applicants only disclose the amino acid sequence of SEQ ID No. 1. Applicants provide no disclosure of what structural feature(s) of the instantly

disclosed polypeptide of SEQ ID No. 1 is responsible for the observed binding to the IL-21 receptor to result in the claimed activity. Given the diversity of the claimed fragments and/or variants of amino acid sequences at least 96.8%, identical to the amino acid sequence according to SEQ ID No. 1, it is incumbent upon the specification to disclose means for identifying such variants commensurate in scope with coverage sought by the claims. Conceivable, a polypeptide that is at least 96.8% identical to SEQ ID No. 1 of 160-aa residues would include, at the most, 5 amino acid changes. However, the changes could locate at any position in the nucleotide sequence encoding SEQ ID No. 1. As there is not recognition of functional structures provided in the present specification for the claimed activity, this may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site for the IL-21 sequence must assume correct structures to be active, which conformation is dependent upon surrounding residues of amino acids of the binding pocket. As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly because the specification does not described the breadth of the polypeptide variants claimed, it would have required undue experimentation to determine alternative sequences meeting the claims requirements that could have the claimed activity.

As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and

physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only one putative functional amino acid sequence, SEQ ID NO: 1, for a polypeptide having the necessary activity, and provides no guidance on determining which polypeptide variants of SEQ ID NO: 1 comprising 1, 2, 3, 4 or 5 amino acid substitutions, deletions or addition that would have an activity of SEQ ID NO: 1.

Response to Applicants' Arguments as they apply to rejection of Claims 5, 8, 10-12, 18, 20 and 32-35 under 35 U.S.C. 112, first paragraph-scope of enablement.

At pages 7 and 8 of remarks, insofar as the claimed genus of IL-21 polypeptide variants, Applicants essentially argue that the specification provides sufficient guidance for amino acid variants of SEQ ID NO:1 containing 160 aa of at least 96% identity to SEQ ID No. 1. Moreover, Applicants allege that support is found in U.S. Patent Application Publication 2003/0003545 (Ebner et al.) for the disclosure of variants that differ from IL-21, but retain the essential properties thereof as Ebner et al. discloses conserved regions of IL-21 polypeptide in Figures 1, 4, 6A- B, and 7, and Tables I-III. Moreover, Applicants allege that at page 6 of Remarks that sufficient guidance is provided in the specification for assays to determine suitable variants

including binding assays, real-time PCR and assays related to signaling pathways induced by binding of IL-21 to its receptor. Such is not persuasive.

The examiner refers applicants to the reasons already of record and the reasons set forth in the paragraphs above.

In relation to the *ex vivo* method of enhancing an immune response in a subject or treating a subject with a deficiency of at least one memory B cell and plasma cell as claimed, Applicants essentially argue that the claims recite that the addition of the memory B cell and plasma cell enhances (i.e. improves) an immune response in a subject. Moreover, Applicants allege that the claims do not preclude that the subject experiences a cell-mediated immune response against an antigen (e.g., viral antigen). Furthermore, Applicants argue that viral antigens can be extracellular antigens against which an immune response in the form of antibodies e.g., against antigens of the viral envelope, would be beneficial as evidenced by the success of clinical trails using antibodies against the viral envelop of hepatitis C and HIV (Joos et al., 2006; Armbruster et al., 2004; Galun et al., 20007). Moreover, Applicants argue that Mascola et al., (2000) and Baba et al., (2000) reported the protection afforded by the introduction of neutralizing Ab against HIV-1 infection. As such, Applicants contend that sufficient disclosure is provided as " The specification discloses that a population of cells (e.g., B cell progenitors) that have been isolated from a subject can be contacted with IL-21 polypeptide or variant thereof, which results in the differentiation of the B cells into plasma cells and/or memory cells, which are then isolated (see, e.g., page 34, line 18, through page 35, line 3; and Examples 3- 5). Furthermore, the specification discloses the administration of the isolated memory B cells and plasma cells to the subject to enhance an immune response (see, e.g., page

34, line 18, through page 35, line 3). Since antibody production (e.g., by plasma cells) is an essential element of the immune response, one of ordinary skill in the art would recognize that the inventive methods would be effective in enhancing an immune response in a subject". Such is not persuasive.

The instant invention broadly embrace enhancing an immune response by administering one or more of a memory B cell and the plasma cell produced *ex vivo* to the subject, including a humoral response against viral antigens of any viral envelope. The art of record discloses a divergent number of microbial infections with different antigenic properties as shown by their mechanism of depressing the immune responses in a subject (Mims et al., Medical Microbiology, 2004; pp 172-177). Though the examiner agrees with applicant that neutralizing monoclonal antibodies in response to immunogenic antigens are sufficient in some viral infections to combat an infectious disease as in the case of Respiratory syncytial virus (Pollack et al., Journal of Infection and Chemotherapy, 2002 pp. 201-206), the instant claims are drawn to methods for inducing an immune response against any viral antigens, including viral infections of a type that is not controlled at all by antibodies such as the in the case of intracellular herpes viruses infections (see, Mims et al., Medical Microbiology, third edition, 2004, pp. 150-152). In addition, monoclonal antibodies such as 2G12, F105, and 2F5 taught by Mascola et al., (2000) and Baba et al., (2000) and reported to provide partial protection against mucosal transmission of HIV-1 or SHIV are hybridoma cell lines secreting antibodies to specific antigenic epitopes of the HIV-1 envelope which are considerably different from the polyclonal antibodies generated in the in a humoral response. There is not evidence that the presence of antibodies in serum (e.g., a memory B cell and a plasma cell) may be directed against relevant or critical viral antigens as

MAb do. Furthermore, there is not evidence that contacting a population of mature B cells and B cell progenitor with IL-21 without exposure to a viral antigen, would be able, when introduced in a subject, to enhance a response against a viral antigen. Despite Applicants' assertions at page 8, "the claims do not preclude that the subject experiences a cell-mediated immune response against an antigen (e.g., viral antigen)" and at page 9, "Since antibody production (e.g., by plasma cells) is an essential element of the immune response, one of ordinary skill in the art would recognize that the inventive methods would be effective enhancing an immune response in a subject", Applicants have not provided any evidences supporting how an immune response against a viral infection is effective e.g., a memory B cell and a plasma cell that are administered back to the subject after isolation, as viruses are intracellular pathogens and an effective response against intracellular viral pathogens involves processing and association of the viral antigen to be presented with the MHC Class I molecule on APC cell surface for activation of T cells to induce a cell-mediated immunity. It is noted that post filing art by Joos et al., teaches monoclonal 2G12 Ab against gp120 of the HIV-1 envelope, and monoclonal Abs 4E10 and 2F5 against gp41. Likewise post filing art by Galun discloses a human monoclonal ab HCV-AB68 against the envelope protein of hepatitis C virus. It is also noted that the state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. > Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application"). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA

1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).

Furthermore, the specification is silent about examples of an *ex vivo* method of treating a subject with a condition characterized by a deficiency of at least a memory B cells and a plasma cells. The specification as filed fails to provide particular guidance to resolve the known unpredictability in the art associated with treatment of an immunocompromised subject. The quantity of experimentation required to practice the methods as claimed would require the *de novo* determination of effective target sites, modes of delivery, safe administration of at least a memory B cells and a plasma cells to target appropriate cells and/or tissues in an immunocompromised subject, and further whereby treatment effects are provided for the claimed condition. Though an enabling disclosure does not required working examples, the instant claims have been examined in accordance with the *Wands* factors and the teachings of the specification as a whole. The *Wands* factors include the presence or absence of working examples and to the extent the instant rejections are not sufficiently supported by an enabling disclosure in combination the nature of the invention, the state of the prior art, the relative skill of those in the

art, the predictability or unpredictability of the art, and the breadth of the claims, the disclosure is not enabling for the breadth of the claims.

New Grounds of Objection/Rejection

Claim objection

Claims 32-35 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 33 which depend from claim 18, is directed to the amino acid sequence of SEQ ID No. 1. However claim 18 embraces the amino acid sequence of SEQ ID No. 1 or a variant of SEQ ID No. 1 comprising 1-5 amino acid substitutions. Thus, the scope of claim 33 extends beyond that of claim 18 from which it depends. Likewise, claim 35 which depend from claim 18, is directed variants of SEQ ID No. 1 comprising 1-5 amino acid substitutions. Thus, the scope of claim 35 extends beyond that of claim 18 from which it depends.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32 and 34 depend from a cancelled claim 1. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Therefore, the metes and bounds of claims 32 and 34 are indefinite.

For the purpose of a compacted prosecution claims 32 and 34 have been interpreted as depending on claim 5.

Conclusion

Claims 5, 8, 10-12, 18, 20 and 32-35 are rejected.

Claims 33 and 35 are objected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633